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ESCHERICHIA COLI SHOCK FOLLOWING CORTICOSTEROID TREATMENT: A PATHOLOGIC STUDY IN BABOONS

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(6) ESCHERICHIA COLI SHOCK FOLLOWING CORTICOSTEROID TREATMENT: A PATHOLOGIC STUDY IN BABOONS.

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Introduction

Experimental models that closely simulate the clinico-pathologic findings in patients with septic shock are being vigorously sought. Using subhuman primates, several laboratories have reported various physiologic, pathologic, and hematologic data which are compatible with those found in the human (6-8, 13, 15-17, 30, 32, 38). In some of the studies, therapeutic interventions have been incorporated (6, 13, 16, 17, 30, 32, 38).

The role of steroids in the treatment of shock remains equivocal. Although steroids have been reported to be beneficial (14, 18, 21, 31, 32, 36, 38, 39, 42, 43, 45), several studies have shown no therapeutic effect of steroid treatment of subhuman primates in shock (13, 30). Recently Schuler et al. (38) has shown that dexamethasone significantly increased the survival rates of endotoxin-treated monkeys whereas Herman et al. (13) have reported that methylprednisolone did not protect the baboon from the lethal effects of intravenously administered live E. coli.

Our laboratory has developed a 24-hour shock model and the effects of live E. coli and endotoxin in the baboon have been described (6, 16). Pathologic studies of septic and endotoxin treated baboons indicated some differences in the lesions observed in the heart, lung, liver, and kidney (6).

This study was designed to determine if corticosteroids would prevent the development of both the pathophysiologic responses and the pathologic lesions of septic shock in baboons treated with live E. coli. The study period was 24 hours. Autopsies were performed to define the pathologic changes of multiple organs and compare the lesions to those previously described in shock in the human (12, 26, 27, 29, 33-35, 37).

Materials and Methods

Twelve baboons (Papio anubis) weighing between 9.6 and 19.1 kg were utilized. The animals were fasted overnight, restrained by a squeeze cage device and administered ketamine hydrochloride (Ketaset) 14 ± 0.5 mg/kg intramuscularly. Cannulation was performed in a femoral vessel and the animals were positioned in a primate restraining chair for a 3-4 hour equilibration period. The awake and alert animals were paired by infusing comparable intravenous doses of live Escherichia coli organisms during a five hour period with one member of each pair receiving methylprednisolone sodium succinate (MP) (Solumedrol). One of the twelve baboons was administered saline in place of organisms.

Three groups were studied. Group A (N=4) received a 2.9×10^{10} organisms/kg mean dose. Group B (N=2) received a 1.9×10^{10} organisms/kg mean dose and 4.4 mg/kg I.M. of gentamicin sulfate (Garamycin). Group C (N=5) received a 5.6×10^{10} organisms/kg mean dose. The baboons given methylprednisolone received bolus injections of 30 mg/kg at 15 minutes following initiation of E. coli organism infusion and subsequent two hour infusions of 15 mg/kg at two

hour intervals. The Group B animals administered the one I.M. dose of Gentamicin sulfate (Garamycin) received the dose 1.5 hours after the total E. coli infusion had been administered. One baboon served as a control and received saline instead of organisms. Arterial pressures, heart rate, temperature, and arterial blood samples for glucose, insulin, hematocrit, white blood cell count, pH, lactate, sodium, potassium, cortisol, serum glutamic pyruvic transamina e (SGPT), and arginase values were determined as reported previously (17).

The baboons were continuously observed for 24 hours, during which time individual animals were sacrificed by Nembutal administration whenever the mean blood pressure fell to 25 mm/Hg. Similarly, at the end of the 24-hour period of observation, all survivors were sacrificed. A summary of the groups, the dose of E. coli, the infused therapy, and the period of survival has been detailed previously (17).

Autopsies were performed immediately upon death of the animals. Tissue samples were taken from the left ventricle, bowel, adrenals, kidneys, liver, lungs, and pancreas within 5-10 minutes after sacrifice. These specimens were rapidly placed in buffered formaldehyde-gluteraldehyde fixative for both light and electron microscopic studies (25). Following procurement of these tissue samples, a thorough examination of all organs was accomplished and additional organ samples were obtained for light microscopic study. Specimens obtained for light microscopy were embedded in paraplast and sections were subsequently stained by hematoxylin and eosin and phosphotungstic acid hematoxylin (PTAH). The tissues

obtained for ultrastructural studies were fixed overnight in the buffered aldehyde fixative, post-fixed in Zetterqvist's fixative, dehydrated in ascending grades of ethanol and embedded in Epon 812 and Araldite. Thin sections were stained with lead citrate and uranyl acetate and examined with an RCA EMU-3G and/or Hitachi HS-9 electron microscope. Examination of tissue samples by light and electron microscopy were conducted without prior knowledge of the experimental treatment.

Results

The results of the metabolic and physiologic findings are reported in detail in the preceding paper (17). In summary, all baboons in Group C given the high dose of organisms died within twelve hours. In Group A two of the four baboons died within eighteen hours while two survived the twenty-four hour period. Both animals in Group B and the one saline-injected control survived for twenty-four hours. The mortality rate in all three groups was not altered by methylprednisolone administration.

Nine of the eleven baboons receiving live E. coli organisms exhibited a characteristic early hyperglycemia. Six of the seven animals dying within the twenty-four hour period showed a progressive hypoglycemia with low mean terminal blood glucose values. Hypoinsulinemia occurred in all experimental baboons within 2-6 hours and was sustained until death. Systemic hypotension was observed although arterial pressures were variable. Potassium and lactate concentrations

increased while pH remained relatively constant in most animals. SGPT and arginase values increased in four of seven baboons dying within eighteen hours.

Autopsy Findings

Gross examination revealed that the pleural, peritoneal, and pericardial cavities contained no increase in fluids in any of the animals examined. Examination of the heart in all the animals revealed no significant gross findings. Examination of the lungs in the twelve baboons revealed a few focal lesions usually found in association with parasitic involvement; there was no appreciable atelectasis or hemorrhage.

The livers of all the experimental animals showed accentuation of the lobules. The gallbladders contained very viscous bile. No pancreatic lesions were noted.

The spleens in all the animals were dark purple in color and invariably appeared small and shrunken. No lesions consistent with acute splenitis were evident.

The adrenals invariably showed gross pathologic changes, although they varied in severity. They appeared brownish-red in color and upon sectioning a brown fluid consistent with hemorrhage could be expressed from the cut surface. Only two animals at autopsy revealed nearly normal-appearing parenchyma, the control animal and one of those given the low dose E. coli plus steroid. No consistent difference in adrenal lesions in the extent or severity of hemorrhage and/or

necrosis, could be appreciated among the various groups.

In the kidneys, the cortices usually showed a pattern of alternating light tan and reddish-brown areas. Occasionally the discolorations appeared wedge-shaped and were felt to be consistent with early incomplete infarcts.

The gastrointestinal tracts were negative except for the stomachs which invariably showed moderate distention with gas.

In summary, the organs showing striking pathologic changes included the adrenal and kidney; minor changes were seen in the lung and liver. No heart, G.I., pancreatic or splenic lesions were discernable grossly. The control animal showed no gross pathologic changes.

Light and Ultrastructural Findings

The only animal in which there were no significant pathologic findings in the liver, kidney, adrenal, lung, or pancreas was the control. The remainder of the animals in this study did show pathologic alterations in several different organ systems. All the specimens were examined for the presence of fibrin thrombi with and without hemorrhage or necrosis and an attempt was made to qualitatively assess the amount of parenchymal damage in each of the organs. Table 1 shows the light microscopic findings and the ultrastructural findings of the

TABLE 1. INCIDENCE AND LOCATION OF FIBRIN THROMBI FOLLOWING LIVE *ESCHERICHIA COLI* ORGANISM INFUSION

		Light Microscopy					Electron Microscopy		
Group	Baboon No.	Liver	Kidney	Adrenal	Lung	Pancreas	Liver	Kidney	Adrenal
A	1	++	+	++	-	-	+	+	+
A	2	+	+++	++	+	+	0	0	0
A	5	++	+	++	-	-	+	+	+
A	6	+	+++	+	+	+	+	+	-
B	3	+	+	-	-	-	-	-	+
B	4	++	+	++	-	-	+	+	+
Control	7	-	-	-	-	-	-	-	-
C	8	+	+++	+	-	-	+	+	+
C	9	-	-	++	-	-	+	-	+
C	10	++	++	+	+	-	+	+	+
C	11	++	++	+	+	-	+	+	+
C	12	++	++	++	+	-	+	+	+

\- - none identified
\+ - minimal number
++ - moderate in number
+++ - large in number

0 - tissues not processed for electron microscopy
\- - fibrin not present
\+ - fibrin present

liver, adrenal, and kidney. No major differences were seen in any of the three groups of treated baboons. Following decoding, an attempt was made to grade the degree of severity in the kidneys, adrenals, and livers of the entire eleven treated baboons. Another reading was done to see if there were any similar or dissimilar patterns among the groups. Following all these reevaluations it was determined that the extent and severity of the organ damage in the groups in the study could not be separated.

The hearts from all twelve animals revealed occasional ectatic vessels, but no fibrin thrombi were present. In some sites an increase of fluid separated the myocardial fibers. There was no necrosis of the myocardial fibers.

Congestive atelectasis was consistently present in the experimental animals. At the alveolar capillary level, moderate numbers of polymorphonuclear leukocytes (polys) were seen. As noted in Table 1, two of the low dose animals and three of the high dose animals did show fibrin thrombi. These were seen as a single thrombus in one of the larger pulmonary arteries or at the arteriolar level. Fibrin deposition was not seen in the capillaries.

With the exception of one of the high dose plus steroid animals, the livers all showed the presence of fibrin thrombi in the sinusoids. The hepatocytes showed vacuolization and occasionally focal hepatocyte necrosis was present. The most typical finding in all of the livers was marked polymorphonuclear leukocyte sequestration within the sinusoids (Figure 1).

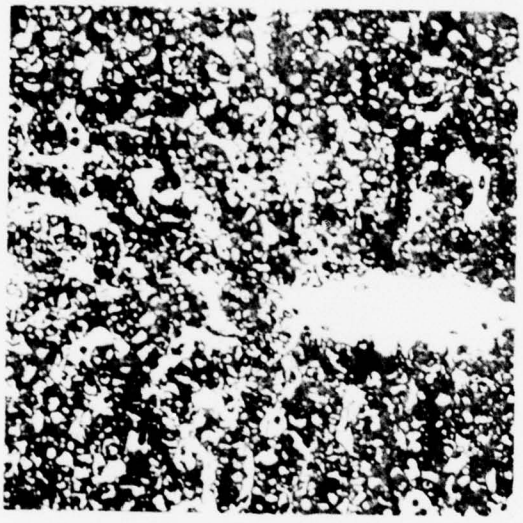

FIGURE 1. Characteristic features in the liver include the presence of polys and fibrin thrombi (arrows) in the actatic sinusoids. The hepatocytes show vacuolization. PTAH; X512.

The hepatic parenchyma showed striking ultrastructural changes. All the animals except two, the saline control and one low dose plus steroid animal, showed sinusoidal fibrin thrombi with underlying endothelial and Kupffer cell damage (Figure 2). In many sites the endothelial cells were lost forming part of the thrombotic mass found within the lumen of the sinusoid. Kupffer cells, when identified, were found to contain massive numbers of bacteria, many secondary lysosomes, and increased numbers of vacuoles. The perisinusoidal space of Disse, lying between the sinusoids and the hepatic parenchymal cells, was decreased in width. The microvilli that normally project from the hepatocytes in this area were lost in many sites. The underlying hepatocytes showed varying degrees of cell injury. Invariably there was some degree of increased cytoplasmic vacuolization (Figure 2). Examination of these vacuoles at higher magnifications revealed that some were membrane limited, but others appeared to be only fluid within the cytoplasmic sap. The mitochondria of the hepatocytes showed some loss of the cristae. A few dilated cisternae of rough endoplasmic reticulum and occasional foci of smooth endoplasmic reticulum were present within the hepatocytes. Occasionally the hepatocytes did not form typical cords with neighboring hepatocytes, and these cell showed marked cytoplasmic organelle damage.

The pancreatic findings in the experimental animals were congestion of the vasculature and decreased basophilic staining of the acinar tissue.

Spleens from all animals showed marked congestion, especially in the red pulp.

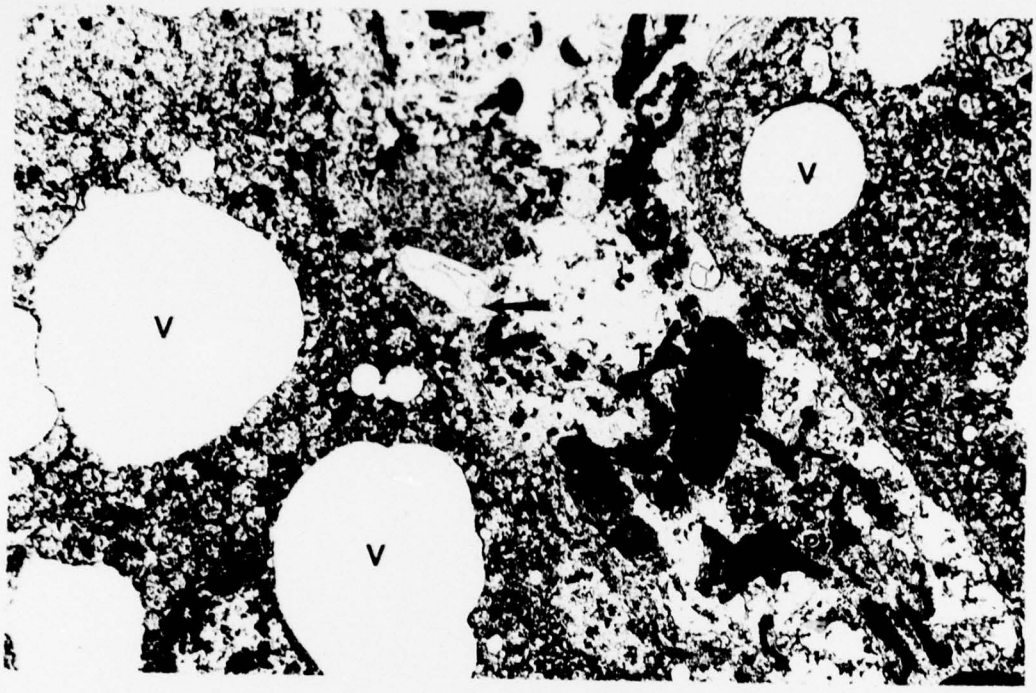

FIGURE 2. The endothelium of the hepatic sinusoid shows fragmentation and desquamation (arrow). Red blood cells, degranulated platelets and polys (P), and strands of fibrin (F) are seen within the sinusoidal lumen. The underlying hepatocytes show blunting of their microvilli, the presence of large vacuoles (V), sparse glycogen granules, and edematous mitochondria. Uranyl acetate and lead citrate; X5600.

Due to the large numbers of laked red blood cells within the sinusoids of the spleen, the PTAH stain for fibrin was unsatisfactory for evaluation.

The adrenal lesion was a very striking finding in this study regardless of the dose of organisms or treatment with the steroid. With the exceptions of animal 6 and the control, the remainder of these animals showed varying degrees of hemorrhage, fibrin thrombi, and parenchymal cellular necrosis (Figure 3). Fibrin thrombi were present usually in association with the hemorrhage. In several of the animals hemorrhage was seen only in the cortex, but generally it involved the cortex and medulla. In several of the baboons, the hemorrhage was severe and the underlying adrenal cortical cells showed severe cell injury and necrosis.

Adrenal specimens for electron microscopic study were separated into blocks from cortex and medulla. In examination of the medulla, the control animal revealed an abundance of cells in which many membrane bounded electron dense granules, 150-350 nm in diameter were seen. Additional cytoplasmic organelles included elongated mitochondria and rough endoplasmic reticulum. Occasionally the Golgi apparatus was seen near the nuclear membrane. In the experimental animals no definitive differences were seen among the low dose, high dose, and antibiotic-treated animal groups. In sites of hemorrhage, cellular edema and an apparent decrease of granules were present (Figure 4).

Cells within the cortices of the experimental animals revealed varying degrees of injury. It was difficult to evaluate the significance of lipid droplets since

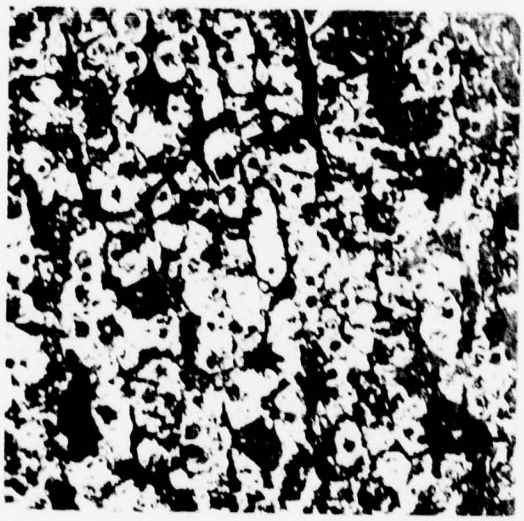

FIGURE 5. Several fibrin thrombi (arrows) are seen in the sinusoids of the zona fasiculata. The underlying cortical cells show marked cytoplasmic edema and several of the cells are necrotic. PTAH; X512.

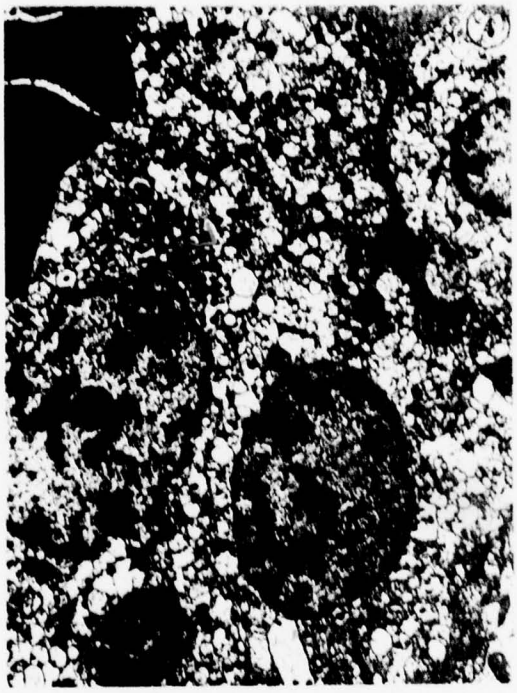

FIGURE 4. The cells within the adrenal medulla show characteristic membrane-limited dense granules. There are increased vacuoles (arrows) in the cells, and the dense granules appear decreased in quantity. Note the extravasated red blood cells (R). Uranyl acetate and lead citrate; X4800.

the zona fasiculata normally contains an abundance of lipid inclusions. Throughout the specimens there was an increase of vacuoles in the cytoplasm and an apparent decrease of the smooth endoplasmic reticulum (Figure 5). A few areas of rough endoplasmic reticulum were found in most of the cells. Occasionally mitochondria showed some "rounding up" rather than their elongate shape as normally found within the reticularis and glomerulosa (Figure 6). The hemorrhage noted by light microscopy was reflected at the E.M. level by large aggregates of red blood cells, strands of fibrin, polys, and platelets (Figure 6). The cortical cells in these sites showed no cell junctions with surrounding cortical cells and showed severe disruption of cytoplasmic organelles.

Renal glomerular and tubular lesions were marked. Only the control and one high dose plus steroid animal did not show glomerular fibrin thrombi. A tubular lesion of varying severity was also evident in these animals consisting of severe vacuolization of the convoluted tubular epithelium with the presence of proteinaceous casts within the tubular lumina (Figure 7).

Ultrastructurally, there were only three animals in which glomerular fibrin thrombi were not present - the control, a low dose plus steroid animal, and a high dose plus steroid animal. All the animals except the control showed varying degrees of tubular cortical injury or necrosis. Ultrastructurally, the glomerular capillaries were ectatic and contained fibrin strands, occasional bacteria, and degenerated poly-platelet elements. The underlying endothelium showed no signi-

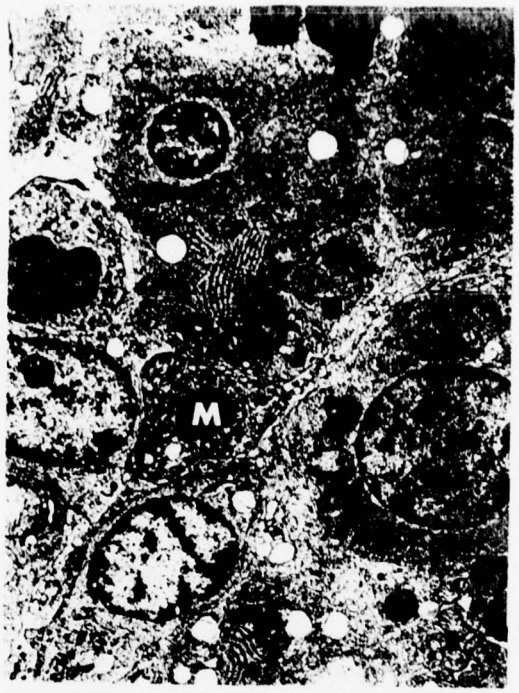

FIGURE 5. Adrenal cortical cells show spherical mitochondria, many of which contain increased numbers of mitochondrial granules. The rough endoplasmic reticulum and lipid droplets are normal. Extravasated RBCs (R) and monocytes (M) are present. Uranyl acetate and lead citrate; X3200.

FIGURE 6. Adrenal cortical cells surround the sinusoid which contains fibrin strands (F), red blood cells, and cellular debris. The cortical cells show spherical mitochondria and cytoplasmic vacuoles (V). One of the cells shows shrunken, dense mitochondria (arrows). Uranyl acetate and lead citrate, X4200.

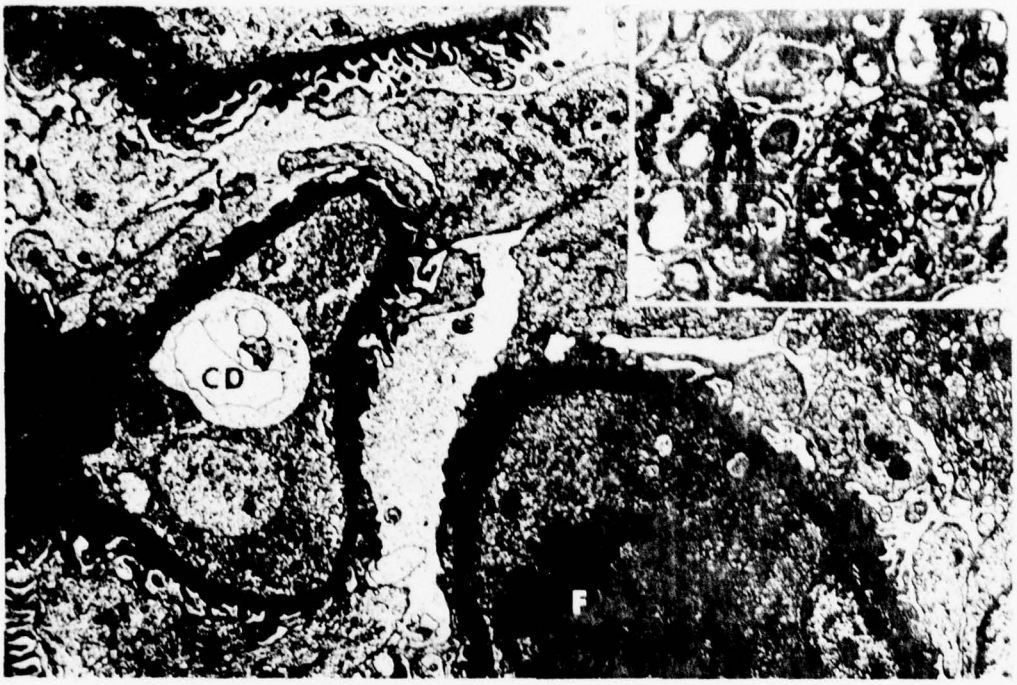

FIGURE 7. The glomerulus contains multiple fibrin thrombi. The surrounding tubules show epithelial vacuolization and increased protein within the lumina. PTAH; X320.

FIGURE 8. The capillaries (C) contain fibrin strands (F) and degenerated cells (DC). The endothelium shows no significant alteration; the epithelium shows mild edema. Uranyl acetate and lead citrate; X5060.

ficant pathological alteration. The overlying epithelial podocytes showed non-specific edema (Figure 8). Examination of the proximal convoluted tubules revealed that the normal brush border shows varying degrees of edema and disruption (Figures 9 and 10). There were increased numbers of lysosomes and often the mitochondria showed edema and/or the accumulation of granules (Figure 10). The complex interdigitations normally seen in the basal half of the cells were disrupted by the increased cytoplasmic edema. The distal convoluted tubules showed focal loss of the few microvilli which project into the lumen and increased vacuolization was seen in the cytoplasm. Occasionlly the vessels between the tubules contained strands of fibrin and various blood cell elements.

The G. I. tract, including esophagus, stomach, duodenum, jejunum, ileum, and several portions of the large bowel, were all examined by light microscopy. The submucosal vessels were ectatic and occasionally showed increased numbers of red blood cells, however, no fibrin thrombi, edema, hemorrhage, or necrosis were present (Figures 11 and 12). The tips of the villi were often congested with red blood cells, but significant epithelial damage was not present in this baboon study.

Sections obtained from the skeletal muscle and skin revealed only one fibrin thrombus in the dermis.

Discussion

Multiple investigators have found evidence that corticosteroids are effective in protecting various animal species and humans against shock induced by endo-

FIGURE 9. The proximal tubular epithelial cells show a prominent brush border (BB). Within the cytoplasm a few increased vacuoles (V) and normal appearing mitochondria are present. Uranyl acetate and lead citrate; X6750.

FIGURE 10. The tubular lumen (TL) contains protein. The microvilli are irregular, edematous, and focally desquamated. The tubular cytoplasm shows increased numbers of lysosomes (L), increased vacuoles (V) and mitochondria which contain multiple dense granules. Uranyl acetate and lead citrate; X6750.

FIGURE 11. The villi of the small bowel show normal height and width, with no significant epithelial degeneration or desquamation. H&E; X200.

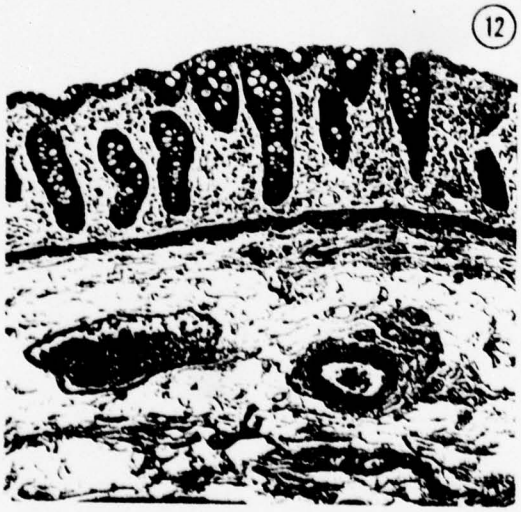

FIGURE 12. The large bowel shows intact epithelium. The vessels within the submucosa show congestion with RBCs but no necrosis is evident. H&E; X200.

toxin and live organisms (14, 18, 21, 31, 32, 36, 38, 39, 42, 43, 45). However, two previous studies in subhuman primates have not shown any protective effect of corticosteroids in septic and/or endotoxin shock (13, 30). The results of this study indicate that there are no differences in the morphologic findings between steroid treated and untreated baboons. These data support our physiologic and metabolic findings (17) and those reported by Herman et al. (13).

In reviewing the studies in which corticosteroids have been shown to have beneficial effects, only one of the studies included a morphologic parameter (45). Wilson (45) has suggested that the endothelial, alveolar epithelial Type I and Type II cellular damage found in the lung in shock can be prevented by the administration of pharmacologic doses of corticosteroids. These findings are at variance with those reported by Pingleton et al. (30) in which no physiologic or morphologic improvement was noted in monkeys with steroid-treated entoxic or hemorrhagic shock. Another study (13) in which bacteremic shock was induced in baboons showed findings comparable to those in our study; they showed that a pharmacologic dose of methylprednisolone failed to protect baboons treated with live E. coli. Although it has been reported that steroids improved cardiac output, regional blood flow, hepatic carbohydrate metabolism, and prevented disseminated intravascular coagulation, in our studies systemic hypotension, hypoglycemia, hypoinsulinemia, liver dysfunction, intrasvascular coagulation, and widespread morphologic alterations were present in steroid-treated animals (17). Further work is definitely indicated to determine the efficacy of steroid treat-

ment in endotoxic versus septic shock models.

Sandritter and Lasch in 1967 (37) reported the pathological aspects of shock in animals and humans. In 1971 McGovern (26) reported that the histologic manifestations of all types of shock in humans were fibrin thrombi in small vessels, hemorrhages, and necrosis of tissues. Subsequently, McGovern (24) reported the histologic manifestations of septicemic shock and found that these included microthrombosis of vessels, especially on the venous side of the circulation, tissue necrosis, and hemorrhages. He pointed out that in gram-negative septicemia there was a greater incidence of pulmonary hemorrhages than in other types of shock. A recent paper by Robboy et al. (34) examined the pathology of disseminated intravascular coagulation and showed that many of the cases in which this phenomenon was found were those with a septic shock basis. The spectrum of pathologic changes reported by this group included major vessel thrombosis, small vessel thrombosis, hemorrhage, and complications thereby induced.

The present study and our previous subhuman primate studies (6, 8, 16) are in agreement with most of the findings reported by McGovern (26, 27). The pathologic changes induced by shock in subhuman primates include edema and/or hemorrhage, fibrin, and necrosis in various systems.

Histologic findings in the baboon reveal no consistent light microscopic cardiac lesion. Although fibrin thrombi are found in many different organ systems, they are rarely, if ever, found in the myocardial vasculature. The myocardial lesion

of transverse tigroid stripes or bands described in hemorrhagic shock (5) are infrequently found in septic or endotoxic shock in baboons.

The pulmonary lesion in this 24 hour study was congestive atelectasis. Although several of the baboons in this study did reveal the presence of fibrin thrombi within the pulmonary vasculature; the thrombi were seen at the arterial level, not at the capillary level. In previous acute septic shock models no fibrin thrombi were found in the pulmonary vasculature (6-8, 30) whereas McKay et al. (28) did report their presence in subhuman primates in acute shock. McGovern (27) has pointed out that hemorrhage is the most consistent pulmonary finding in septic patients. In his series, only two of thirty-four autopsy subjects had thrombi within the pulmonary vasculature. Remmele and Harms (33) have suggested that if the shock patients died within 24 hours, thrombi were usually found within the pulmonary vessels. The variation reported between human and animal series could probably be explained on the basis of endotoxin and/or live organism dosages, infusion rates, and clot lysis times, but numerous other possibilities undoubtedly exist.

The hepatic findings in our study include sinusoidal fibrin strands or thrombi and/or polys at the light microscopic and/or ultrastructural level. The finding of the fibrin thrombi in the sinusoids of the liver has been consistent in several studies involving baboons with either endotoxin or live E. coli shock (6, 19). Frequently they are not definitely identified light microscopically, but are a consistent finding at the ultrastructural level. This finding in sub-

human primates does not agree with those reported by McGovern (27) in humans in which fibrin thrombi and hemorrhages were not reported; only cellular necrosis was described. Remmele and Harms (33) described fibrin thrombi in patients with shock who die within 24 hours, and they have been recognized in other experimental shock studies involving multiple species (1, 23, 44). The most consistent finding in the liver in septic shock in primates is that of polymorphonuclear leukocytes in the hepatic sinusoids.

Renal glomerular fibrin thrombi were found with remarkable consistency in the baboons. Only one of the experimental animals did not have fibrin thrombi within the glomerular capillaries. The finding of glomerular fibrin thrombi in the live E. coli baboon model differs from the endotoxin treated baboon in which at 18 to 24 hours no glomerular fibrin thrombi are seen (6). The same variation of the presence of renal thrombi is reflected in the human literature. McGovern (27) reported that the most frequent lesion was tubular necrosis with thrombi seen in three of six of the patients examined whereas Robboy et al. (34) have shown that the kidney is the most frequently involved organ in DIC. In the septic patients in their series the kidney is noted to be frequently involved by glomerular fibrin thrombi. The tubular lesion in shock is probably the most consistent renal pathologic finding (3, 26, 27). The degree of tubular damage can vary considerably, from simple vacuolization of the proximal convoluted tubules to bilateral cortical necrosis. In this study there was some degree of tubular damage in all of the experimental animals. The ultrastructural findings are nonspecific and indicate cell injury; they have been described in hypoxic and

ischemic models.

The adrenal gland lesions have not been previously described in the baboon in shock. In this study all animals, except the control, showed fibrin thrombi at either the light or ultrastructural level. All animals had varying degrees of hemorrhage and/or cellular necrosis. The thrombi and hemorrhages were seen most frequently in the cortex, but in some animals the medulla was also involved. The findings in this study are identical to those described by Hoffmann (20) in calves dying from endotoxin shock and by Russell (35) who studied the adrenal gland changes in patients with shock as hemorrhage, necrosis, and intravascular thrombosis. He points out that hemorrhage can range from small zones of red cell extravasation to massive hemorrhage and the necrosis can range from focal cytolysis and cell degeneration to complete cortical infarction. In describing the intravascular thrombi he points out that central vein thrombosis and small fibrin thrombi in sinusoids were predominant patterns. In our study the small thrombi were present primarily in the sinusoids of the zona fasciculata whereas Russell has reported the thrombi in the human to be frequently found in the zona glomerulosa. Other studies in humans also support the conclusion that small fibrin thrombi are present in the adrenal glands in shock patients (26, 27, 33). There was no correlation of the extent of adrenal pathology with steroid treatment or non-treatment, nor was there any correlation with the extent of damage to the circulating catecholamine levels in the three groups in this study (17).

The gastrointestinal findings were of special interest in this study. McGovern

(27) has shown that the intestine is the third most commonly involved system in the human, the characteristic lesion being acute ischemic enterocolitis. Moon (29) has stated that hyperemia, edema, and focal hemorrhages are the characteristic lesions of shock in the G.I. tract. Other authors have described a hemorrhagic necrotizing or pseudomembranous necrotic alteration within the intestine or a submucosal vascular lesion (12, 22). A longstanding controversy in the shock field is the response of the dog gut following endotoxin or live organism shock (2, 11, 24). Over the years, Fine (9, 10) has supported the concept that substances escaping from the ischemic gut into the systemic circulation establishes a circumstance by which shock is perpetuated regardless of the original etiology. It is recognized that the mesenteric responses to endotoxin differ in the dog and the baboon (2, 40, 41). The only significant hemodynamic change in the primate small and large intestines is a lowered vascular resistance. Our study in the primate would indicate that the G.I. tract does show some intravascular congestion but no hemorrhage or ischemic necrosis is present, a finding unlike that found in the dog (4). Our only G.I. "lesion" was that occasionally the small capillaries in the villus tips showed ectasia and increased numbers of red blood cells, but no overlying ischemic necrosis was present light microscopically. Ultrastructural studies would have to be done to determine if hypoxic changes are present in the epithelium overlying the villus tips.

The findings in this study would suggest that the baboon subjected to low or high doses of live E. coli organisms and followed for a period of 24 hours re-

ceived no significant beneficial effect from the administration of adrenocorticosteroids as determined by morphologic parameters. Further, the subhuman primate baboon does show anatomic lesions in multiple organs which are comparable to those described for the human in shock.

Summary

The purpose of this study was to determine if corticosteroids would prevent the development of the pathologic lesions of septic shock in baboons treated with live E. coli organisms during a 24-hour study period. Pathologic changes were defined for multiple organs and compared to the lesions previously described in shock in humans. Eleven awake baboons were infused with comparable doses of live E. coli organisms during a five hour period with one member of each pair receiving methylprednisolone. One additional animal received saline in place of organisms and served as a control. Autopsies were performed immediately and specimens were obtained from the heart, lungs, liver, adrenals, kidneys, pancreas, and G.I. tract for light and ultrastructural studies.

Results of this study would indicate that adrenal corticosteroids do not prevent and/or decrease the severity of any of the morphologic lesions in the baboon subjected to low or high doses of E. coli organisms. The pathologic changes induced by live E. coli organisms in the baboon include fibrin thrombi, edema and/or hemorrhage, and necrosis of multiple organ systems. The liver, adrenal, and kidney show striking pathologic changes whereas the gastrointestinal tract shows no significant pathologic alteration. This morphologic study demonstrates that the shock lesions of the subhuman primate and human are remarkably similar.

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